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Associations between Long-Term Exposure to Chemical Constituents of Fine Particulate Matter (PM_{2.5}) and Mortality in Medicare Enrollees in the Eastern United States

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Running title: Exposure to PM_{2.5} constituents and mortality

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Abstract

Background: Several epidemiological studies have reported that long-term exposure to fine particulate matter (PM_{2.5}) is associated with higher mortality. Evidence regarding contributions of PM_{2.5} constituents is inconclusive.

Objectives: We assembled a dataset of 12.5 million Medicare enrollees (≥ 65 yrs) to determine which PM_{2.5} constituents are: 1) associated with mortality controlling for previous-year PM_{2.5} total mass (main effect); and 2) elevated in locations exhibiting stronger associations between previous-year PM_{2.5} and mortality (effect modification).

Methods: For 518 PM_{2.5} monitoring locations (Eastern US, 2000-2006), we calculated monthly mortality rates, monthly long-term (previous 1-year average) PM_{2.5}, and 7-year averages (2000-2006) of major PM_{2.5} constituents [elemental carbon (EC), organic carbon matter (OCM), sulfate (SO₄²⁻), silicon (Si), nitrate (NO₃⁻), and sodium (Na)] and community-level variables. We applied a Bayesian hierarchical model to estimate location-specific mortality rates associated with previous-year PM_{2.5} (model level 1) and identify constituents that contributed to the spatial variability of mortality, and constituents that modified associations between previous-year PM_{2.5} and mortality (model level 2), controlling for community-level confounders.

Results: One standard deviation (SD) increases in 7-year average EC, Si, and NO₃⁻ concentrations were associated with 1.3% [95% posterior interval (PI): 0.3, 2.2], 1.4% (95% PI: 0.6, 2.4), and 1.2% (95% PI: 0.4, 2.1) increases in monthly mortality, controlling for previous-year PM_{2.5}. Associations between previous-year PM_{2.5} and mortality were stronger in combination with 1-SD increases in SO₄²⁻ and Na.

Conclusions: Long-term exposures to PM_{2.5} and several constituents were associated with mortality in the elderly population of the Eastern US. Moreover, some constituents increased the association between long-term exposure to PM_{2.5} and mortality. These results provide new evidence that chemical composition can partly explain the differential toxicity of PM_{2.5}.

Introduction

Regulatory control of particulate matter (PM) could be dramatically improved with robust quantification of the evidence regarding the toxicity of various constituents of the PM mixture and of their sources (Science Advisory Board, U.S. Environmental Protection Agency (EPA), 2004). Currently, PM is regulated based on the total mass concentration without regard to its chemical composition, but scientific evidence on which types of constituents are most harmful could result in more effective regulations. However, the knowledge regarding differential toxicities of PM constituents has been identified as a crucial research gap (National Research Council, 2004).

Responding to the need for such evidence, for the last decade, data have been accumulated for the constituents of fine particulate matter (PM_{2.5}) nationwide in the US and have provided opportunities for studying the association between morbidity/mortality risk and PM_{2.5} constituents. Using these data, numerous epidemiological studies have reported evidence of health effects associated with PM_{2.5} constituents, both in short-term (a few days previous) and long-term (a few years previous) exposure timeframes. Studies focusing on the short-term health effects include Bell et al. (2014), Cao et al. (2012), Ito et al. (2011), Kim et al. (2012), Levy et al. (2012), Ostro et al. (2009), Peng et al. (2009), and Zhou et al. (2011). Fewer studies have investigated the long-term health effects of different PM_{2.5} constituents including Dockery et al. (1993), Ostro et al. (2010), and Pope et al. (1995; 2002). However, studies have not reported consistent findings regarding associations with specific constituents. Such discrepancies may be because of different aspects of the study design (e.g., population, confounding control, timeframe, and statistical analysis) and the EPA has called for further research (U.S. EPA, 2009).

To fill this research gap, we investigated the differential toxicity of long-term $PM_{2.5}$ exposure according to its chemical composition based on a large-scale national database including approximately 12.5 million Medicare enrollees (≥ 65 yrs). Combining several sources of data, we constructed a monthly multi-site time series dataset for 518 $PM_{2.5}$ monitoring locations in the Eastern region of the US during 2000–2006. The data include, for each monitoring location, monthly mortality rates, monthly values of the average $PM_{2.5}$ concentration over the previous 12 months, 7-year average concentrations of $PM_{2.5}$ constituents, and community-level confounding variables on socio-economic status (SES) and racial composition. Using a Bayesian hierarchical (BH) regression model, we estimated spatially-varying (SV) mortality rates associated with previous-year $PM_{2.5}$ and identified chemical constituents that explained the spatial variability of the mortality rates, controlling for $PM_{2.5}$ and community-level characteristics.

Methods

Data Description

$PM_{2.5}$ total mass

We obtained daily (24-hour average) concentrations of $PM_{2.5}$ at 518 monitors in the Eastern US (Figure 1) for 2000–2006 from the EPA Air Quality System (AQS) database (U.S. EPA, 2014). Using the daily $PM_{2.5}$ data, we calculated monthly long-term exposure to $PM_{2.5}$ as described in detail in Greven et al. (2011). In brief, for the first day of every month and at each of the 518 monitor locations, we calculated previous 1-year average of daily $PM_{2.5}$ concentrations (x_{ij}) for i th monitor at j th month with $i = 1, \dots, n$ and $j = 1, \dots, n_i$. Because not all monitors had valid measurements for the entire study period, the number of monthly $PM_{2.5}$ values at a given monitoring location (n_i) varied from 33 to 70.

PM_{2.5} chemical constituents

Although the US EPA measures over 50 PM_{2.5} chemical constituents, we focused on 6 identified in previous research as contributing substantially to PM_{2.5} total mass (Bell et al. 2007): elemental carbon (EC), organic carbon matter (OCM), sulfate (SO₄⁼), silicon (Si), nitrate (NO₃⁻), and sodium (Na). We obtained 7-year averages of the 6 chemical constituents at 174 monitors in the Eastern Region for 2000–2006 from the EPA AQS database, as described in detail elsewhere (Bell et al. 2007).

One challenge in our study is that the PM_{2.5} constituents are measured at monitors (174 monitors) that are not collocated with the PM_{2.5} monitors (518 monitors) (Figure 1). We assumed that the levels of constituents are spatially homogenous within a 6-mile radius, and therefore linked PM_{2.5} monitors to PM_{2.5} constituent monitors within 6 miles. Out of the 518 PM_{2.5} monitors, 241 had PM_{2.5} constituent monitors within 6 miles and we assigned 7-year averages of each PM_{2.5} constituent of the closest constituent monitor to each of 241 PM_{2.5} monitor. For the remaining 277 monitoring locations, we treated the levels of PM_{2.5} chemical constituents as missing and applied a statistical approach to impute the missing data, as described in Statistical Methods. For either measured or imputed values, we let $z_i = (z_{i1}, \dots, z_{i6})'$ denote the 7-year average concentrations of the 6 chemical constituents for i th PM_{2.5} monitor location.

Mortality count and total number of people at risk

Mortality counts and the total number of people at risk were obtained at zip-code level from billing claims of Medicare enrollees who are fee-for-service Medicare beneficiaries (aged ≥ 65 years) (Greven et al. 2011). For each of the 518 PM_{2.5} monitor locations, we calculated monthly numbers of deaths and people at risk among the Medicare enrollees residing in each zip-code

with a centroid < 6 miles from a $PM_{2.5}$ monitor location. Depending on the location, 6-mile buffers around the monitors included the centroids of at least 3 and up to 20 different zip codes and the data were aggregated over 3-20 zip-codes. We let Y_{ij} and N_{ij} denote the number of deaths and the people at risk for i th monitor location at j th month. For the whole study period across all 518 locations, the total size of the study population was 12.5 million enrollees with the total number of deaths equal to 2.2 million approximately residing in 4,974 zip-codes. For the 241 locations with $PM_{2.5}$ constituent data available, 1.2 million deaths occurred among 7.5 million enrollees approximately living in 3,425 zip-codes.

Community-level confounders

We obtained zip-code level data on community-level confounding variables including SES and racial composition from the US Census 2000 (US Census Bureau, 2000). We averaged values over all zip-codes with centroids within 6 miles of each $PM_{2.5}$ monitor and assigned the averaged value to each monitor. We let $w_i = (w_{i1}, \dots, w_{i5})'$ denote the 5 community-level confounders: median family income, proportion of people with high-school diploma or equivalent, proportion of residents in urban environment, proportion of white residents, and proportion of black residents.

Statistical methods

We analyzed the linked data using a BH Poisson regression model. The first level, a Poisson regression model with spatially varying (SV) random effects, was used to estimate the association between month-to-month variation in mortality rate and month-to-month variation in long-term (previous 1-year average) $PM_{2.5}$:

$$Y_{ij} \sim \text{Poisson}(\lambda_{ij}), i = 1, \dots, n \text{ and } j = 1, \dots, n_i,$$

$$\text{Log}(\lambda_{ij}) = \log(N_{ij}) + \alpha_{i0} + \alpha_{i1}x_{ij}^*, \quad [1]$$

where Y_{ij} and N_{ij} are the number of deaths and the size of the population at risk for the i th monitoring location and j th month, x_{ij}^* is the previous-year average $\text{PM}_{2.5}$ centered around the location-specific average (i.e., $x_{ij}^* = x_{ij} - \bar{x}_i$), and α_{i0} and α_{i1} are the location-specific (spatially-varying) random intercepts and slopes. The parameter α_{i0} represents the SV baseline mortality rate when the previous-year average $\text{PM}_{2.5}$ is equal to its location-specific average (i.e., $x_{ij}^* = 0$). The parameter α_{i1} represents the SV association between month-to-month variation in mortality rate and month-to-month variation in previous-year $\text{PM}_{2.5}$.

The second level of the BH model regresses the location-specific 7-year averages of $\text{PM}_{2.5}$ constituents and community-level confounders on the SV intercept and slope, α_{i0} and α_{i1} :

$$\alpha_{i0} = \beta_0 + \sum_{k=1}^6 \beta_k z_{ik}^* + \sum_{l=1}^5 \beta_{6+l} w_{il}^* + \beta_{12} \bar{x}_i + \varepsilon_{i0} \quad [2]$$

$$\alpha_{i1} = \gamma_0 + \sum_{k=1}^6 \gamma_k z_{ik}^* + \sum_{l=1}^5 \gamma_{6+l} w_{il}^* + \varepsilon_{i1}, \quad [3]$$

where z_{ik}^* is the level of the k th chemical constituent and w_{il}^* is the l th community-level confounder at i th location, and ε_{i0} and ε_{i1} are random errors. We centered and scaled all explanatory variables to simplify interpretation and reduce multi-collinearity. Note that \bar{x}_i is included in the SV intercept model [2] to control for total $\text{PM}_{2.5}$ concentration when estimating the effects of constituents on the spatially-varying mortality rate (Mostofsky et al. 2010).

To account for potential residual spatial correlation in the second level, we assumed the error terms could be spatially correlated using a standard approach (Gelfand et al. 2003) (see Supplemental Material, Accounting for residual spatial correlation). We fit our BH model using

a Monte Carlo Markov Chain (MCMC) method (see Supplemental Material, “Two-stage estimation and the Markov Chain Monte Carlo (MCMC) algorithm”). All computations were conducted using R statistical software (<http://www.r-project.org>).

There are four sets of parameters of interest. From the first level [1], we obtained 1) the SV (i.e., monitor-specific) baseline mortality rates when the previous-year $PM_{2.5}$ was equal to its monitor-specific overall average (SV intercepts α_{i0} for each location i , expressed as deaths/month/1,000 persons); and 2) the SV association between month-to-month variation in mortality rate and month-to-month variation in previous-year $PM_{2.5}$ (SV slopes α_{i1} for each location i , expressed as the percentage increase in the mortality rate associated with a $1\text{-}\mu\text{g}/\text{m}^3$ increase in previous-year $PM_{2.5}$). From the second level [2]-[3], we obtained 3) the association between the SV intercepts and the monitor-specific 7-year averages of $PM_{2.5}$ constituents, adjusted by community-level confounders and previous-year $PM_{2.5}$ (the β_k coefficients from [2], expressed as the percentage increase in the mortality rate associated with a 1-SD increase in the 7-year average concentration of each constituent), and 4) the association between the SV slopes and the monitor-specific 7-year averages of $PM_{2.5}$ constituents, adjusted by community-level confounders (the γ_k coefficients from [3], expressed as the percentage increase in the mortality rate ratio for previous year $PM_{2.5}$ associated with a 1-SD increase in the 7-year average concentration of each constituent).

To find the best fit for the second level model, we conducted an extensive sensitivity analysis. We considered the following 8 models: no explanatory variable, constituents only, community-level confounders only, or both constituents and community-level confounders as explanatory

variables, all with and without spatially correlated errors. Among the 8 options, we chose the best fit based on the Deviance Information Criteria (DIC) (Spiegelhalter 2002).

There were 277 PM_{2.5} monitoring locations with missing values for the constituents. Separately for each constituent, we fit a Bayesian spatial Gaussian process (GP) model based on the observed data (i.e., 241 locations) and estimated a spatial correlation using the spBayes R package (Finley et al. 2007) and imputed the missing values based on the posterior predictive sample means for the 277 PM_{2.5} monitors (see Supplemental Material, Bayesian spatial Gaussian process (GP) for missing imputation) Prior to using the imputed constituent levels in the analysis, we confirmed that the Bayesian spatial GP modeling was appropriate for imputation via a cross-validation (CV) study (see Supplemental Material, Cross validation study).

We conducted the analysis for the complete case data (n=241 monitoring locations with the data available for both PM_{2.5} total mass and the chemical constituents) and for the all sites data (n=518 monitoring locations using imputed values for the 277 locations without measurements for PM_{2.5} chemical constituents). Also, we analyzed the data for the entire elderly population (≥ 65 yrs) and stratified by two age groups (65-74 yrs versus ≥ 75 yrs).

Results

Table 1 reports summary statistics for each variable for the complete case data (n=241) and for the all sites data (n=518). Figure 2a displays maps of 7-year averages of PM_{2.5} exposure levels ($\mu\text{g}/\text{m}^3$) and Figure 2b presents maps of 7-year averages of mortality rates (deaths/month/1000persons) for 518 monitoring locations. Figure 3 shows maps of 7-year averages of each chemical constituent ($\mu\text{g}/\text{m}^3$) for the 241 locations with available data. SO₄⁼

and NO_3^- levels seem to exhibit strong spatial correlations; OCM, Si, and Na levels moderate spatial correlations; and EC levels weak spatial correlations with high values only in a few locations. Estimated spatial correlations were obtained from the spatial GP model between pairs of monitors with a distance of about 40 miles are 0.05, 0.20, 0.21, 0.19, 0.21, 0.20 for EC, OCM, $\text{SO}_4^{=}$, Si, NO_3^- , and Na, respectively. All 5 community-level confounders are also spatially mapped (Figure S1) over the 518 locations.

The correlations among the 7-year averages of $\text{PM}_{2.5}$ total mass, the $\text{PM}_{2.5}$ chemical constituents and community-level confounders are summarized in Table S1 for the complete case data ($n=241$). We observed that $\text{PM}_{2.5}$ is correlated positively with OCM (0.43), $\text{SO}_4^{=}$ (0.61), and the proportion of black residents (0.32) and inversely with Na (-0.41). The highest positive correlations among the constituents were observed between EC and OCM (0.44), $\text{SO}_4^{=}$ and OCM (0.41), and Si and OCM (0.43). Among the community-level confounders, strong positive correlations were observed as 0.62 between median family income and the proportion of people with high school diploma or equivalent and 0.50 between the proportions of white residents and high school graduates, whereas the strongest negative correlation was -0.84 between the proportions of white and black residents. Between the constituents and the community-level confounders, the highest correlations were observed for OCM at 0.39 and for Si at 0.34 with the proportion of black residents.

Prior to the BH regression modeling, we conducted cross-validation (CV) studies for our imputation method for the missing constituent levels. The sample correlation coefficients between the observed and predicted values for the test data are 0.64-0.94 for all constituents averaged over 5 CV datasets (Supplemental Material, Table S2). The Root Mean Squared Error

(RMSE) for prediction for each constituent and the average RMSE over 5 CV datasets is about half of the sample standard deviation for all constituents (Supplemental Material, Table S3). Scatter plots for the observed vs. predicted data show that the points generally follow the reference line (meaning observed values = predicted values) (Supplemental Material, Figure S2). Based on the CV study results, we concluded that the Bayesian spatial GP method was appropriate for imputing the missing constituents in our study.

We analyzed the complete case data (n=241) and the all sites data (n=518), separately. We fit Equations [1], [2], [3], and Supplemental Material, Equation [S1] with 8 different options and chose the best fit based on the smallest DIC (Supplemental Material, Table S4). We obtained the smallest DIC for the model including both chemical constituents and community-level confounders as explanatory variables and with spatially independent errors both for the SV intercept and slope model in complete case data as well as in the all sites data.

Figures 4a and 4b display results from the first level of the BH model for complete case data (left panels) and all sites data (right panels), respectively. Both data showed similar results. Figure 4a shows the estimated monthly mortality rate when the previous-year $PM_{2.5}$ is equal to its monitor-specific overall average ranges from 3.37 to 6.15 (deaths/month/1000persons) over the study region from all sites data analysis. Also, Figure 4b shows the estimated association of mortality rate with 1 $\mu g/m^3$ increase in the previous-year $PM_{2.5}$ is from -1.0 to 4.6 (% increase in mortality rate).

Figure 5a and 5b report the results from the second level of the BH model for complete case data (left-solid bars) and all sites data (right-dashed bars), respectively. Results were similar between complete case data and all sites data, but the all sites estimates were somewhat smaller and their

confidence intervals are narrower. In both analyses, we observed that adjusting for the community-level confounders and $\text{PM}_{2.5}$ total mass, EC, Si, and NO_3^- were positively associated with mortality rate (the SV intercept, β_k) while $\text{SO}_4^{=}$ was inversely related to mortality (Figure 5a). Meanwhile, SV slope estimates (γ_k) indicated that the percentage increase in mortality rate with a 1-unit increase in average previous-year $\text{PM}_{2.5}$ was greater than expected when combined with a 1-SD increase in $\text{SO}_4^{=}$ and Na (Figure 5b).

Finally, we analyzed the data stratified by two age groups (65-74 yrs versus ≥ 75 yrs). For the SV intercept model (Supplemental Material, Figure S3), results for younger age group were similar to those for the all age analysis (i.e., main effect estimates for EC, Si, and NO_3^- were significant) whereas for the SV slope model (Supplemental Material, Figure S4), both age groups (65-74 and ≥ 75 yrs) had results similar to those for all age analysis (≥ 65 yrs).

Discussion

We investigated: 1) whether month-to-month changes in mortality rates were associated with month-to-month changes in the previous-year average exposure to $\text{PM}_{2.5}$; and 2) whether 7-year average levels of $\text{PM}_{2.5}$ chemical constituents modified this association.

For the SV intercept, EC, Si, and NO_3^- were positively associated with mortality rates after adjusting for $\text{PM}_{2.5}$ total mass and the community-level confounders. For EC, our results are consistent with a previous cohort study of female public school professionals in California (Ostro et al. 2010). Evidence for the toxicity of Si was also found in other studies. Ostro et al. (2010) reported that long-term exposure to Si was positively associated with pulmonary mortality. Si may serve as a surrogate for toxic constituents found in mineral dust associated with traffic

(Moreno et al. 2013; Reff et al. 2009). A previous study reported that long-term exposure to traffic or traffic-related pollutants is associated with cardiopulmonary mortality (Jerrett et al. 2005). Few studies examined associations for NO_3^- with mortality in a long-term framework. Ostro et al. (2010) reported that long-term exposure to NO_3^- was significant for mortality in a single pollutant model but not in a multi-pollutant model. Additionally, $\text{SO}_4^{=}$ was found to be inversely associated with mortality rates, which is inconsistent with previous studies where positive associations were found (Dockery et al., 1993; Ostro et al. 2010; Pope et al., 1995, 2002). While the observed positive associations were from single pollutant approaches, our study uses a multi-pollutant analysis also including adjustment for the $\text{PM}_{2.5}$ total mass and community-level confounders. Therefore, the inverse associations that we observed should be interpreted with caution, as they may be an artifact of multi-collinearity resulting from correlations between $\text{SO}_4^{=}$ and other constituents, $\text{PM}_{2.5}$ total mass, and community-level confounders.

$\text{SO}_4^{=}$ and Na were significant modifiers of monitor-specific associations between previous-year average $\text{PM}_{2.5}$ and mortality rates. Previous long-term exposure studies for $\text{PM}_{2.5}$ constituents have reported significant positive associations of $\text{SO}_4^{=}$ with all-cause mortality (Dockery et al. 1993; Pope et al. 2002) or with cardiopulmonary mortality (Ostro et al. 2010; Pope et al. 2002). Na was also a significant modifier that strengthened the association between long-term $\text{PM}_{2.5}$ and mortality. Few studies have estimated associations between Na and health outcomes, with some showing evidence of associations with mortality (Krall et al. 2013) or hospital admission (Zanobetti et al. 2009).

Several possible mechanisms have been proposed in human subject studies linking constituents to biomarkers: systemic inflammation and oxidative stress associated with EC (Neophytou et al.

2013), altered DNA methylation related to Si (Hou et al. 2014), and inflammation related to NO_3^- , and $\text{SO}_4^{=}$ (Wu et al. 2012). However, because of limited evidences from experimental/toxicological studies, the biological pathway through which short-term exposure to $\text{PM}_{2.5}$ and its components affect health is still an area of active investigation, and the mechanisms for long-term exposure are less understood.

The US EPA measures over 50 different chemical constituents. Analyzing all available constituents would present problems of multiple comparisons. We selected the 6 constituents that were previously shown to be the largest contributors to $\text{PM}_{2.5}$ total mass and/or co-vary with $\text{PM}_{2.5}$ total mass (Bell et al. 2007). Also, the reliability of a community-level average of $\text{PM}_{2.5}$ constituent exposure varies by constituent. For the 6 constituents investigated in the present study, the average correlation of monitors in close proximity (<5km) ranges from 0.60 to 0.93 and for larger distances (20-50km) ranges from 0.46 to 0.88 (Bell et al. 2011). The spatial heterogeneity of many other constituents may be larger, limiting the interpretation of community-level exposures. However, we recognize that other constituents have also been found to be associated with human health. In particular, associations of health outcomes with $\text{PM}_{2.5}$ metal constituents that were not included in our analysis, such as aluminum (Al), calcium (Ca), chromium (Cr), lead (Pb), manganese (Mn), nickel (Ni), titanium (Ti), vanadium (V), and zinc (Zn), have been reported in previous studies (Bell et al. 2014; Cavallari et al. 2008; Hsu et al. 2011; Lippmann et al. 2006; Wu et al. 2012).

One limitation of the available air pollution data is that monitors that measure $\text{PM}_{2.5}$ total mass and monitors that measure the $\text{PM}_{2.5}$ chemical constituents are misaligned (Figure 1). We addressed this limitation by assuming that ambient levels of $\text{PM}_{2.5}$ constituents were

homogeneous within a 6 mile radius. This spatial homogeneity assumption for air pollutants builds on a previous research (Bell et al. 2011) where 6 miles (about 10km) in radius is a reasonable buffer size for the homogeneity assumption. In Bell et al. (2011), the estimated spatial correlations between pairs of monitors with distances of 5-10 km are 0.67, 0.85, 0.95, 0.62, 0.95, 0.59 for EC, OCM, $\text{SO}_4^{=}$, Si, NO_3^- , and Na, respectively. However, spatial variability varies by constituent, for example with more heterogeneity for Si or Na than for $\text{SO}_4^{=}$ or NO_3^- , and different buffer sizes may be applied for different constituents when aligning various sources of data.

Another limitation for air pollution data is that monitors that measure $\text{PM}_{2.5}$ total mass are much denser than monitors that measure $\text{PM}_{2.5}$ chemical constituents (Figure 1). When we aligned the two kinds of monitors, missing data occurred for almost half of the $\text{PM}_{2.5}$ monitors. To avoid simply removing the observations with missing values and reducing the sample size to half, we adopted a Bayesian spatial GP modeling and conducted a single value imputation for the missing data separately for each constituent. We compared the results between the complete case data analysis and the all sites data analysis with the imputed values. Although imputation did not change our primary conclusions, results based on the imputed data should be interpreted with caution. Specifically, using a single-value imputation does not incorporate uncertainty for prediction and measurement error can occur for the explanatory variables in regression modeling (Gryparis et al. 2009).

In our study, the PM data are the ambient levels, which we use to approximate the actual human exposure. The ambient level of a given pollutant is not a perfect surrogate of personal exposure to that pollutant, which can induce exposure measurement error into the analysis with variations

in error by constituent. Although in a multi-pollutant analysis such as the present study, this type of errors may induce upwards bias in regression coefficient estimates, resulting in anti-conservative inference on health effects, several authors have shown that this type of bias barely occurs in situations in which the amount of error or the correlations among pollutants in analysis are extremely large (Schwartz and Coull 2003). Therefore, it is unlikely that differences between ambient levels and personal exposures explain the observed associations in our study.

Our analysis is based on a multi-site time-series data where long-term exposure was estimated by calculating previous 1-year average of daily exposure values at each temporal point (i.e. first day of each month). However, results may be sensitive to different choices of timeframes. Kim et al. (2012) reported that different lag values should be selected for the short-term effects of PM_{2.5} constituents depending on health outcomes. Shorter or longer timeframes than a year could be considered for examining long-term health effects of PM_{2.5}.

Our study focused on the Eastern Region of the US and our findings may not be generalizable to other areas because the characteristics of PM mixtures and populations are quite different across the US (Bell et al. 2007), and effect modification by the chemical composition of PM_{2.5} may vary among regions. Also, we focused on the elderly population, which may be more susceptible to effects of exposure than other age groups. In our study, slight differences in results were found between two age groups (65-74 yrs and ≥ 75 yrs).

To our knowledge, this is the first large-scale study (covering the Eastern US) investigating the association between long-term exposure to PM_{2.5} and mortality rate and effect modification by the chemical constituents of PM_{2.5}. Unlike previous studies of PM_{2.5} constituents, we used a BH

regression approach, where $PM_{2.5}$ constituents were modeled as potential modifiers of the main effect of $PM_{2.5}$ on health outcomes. Despite limitations, our findings add new evidence regarding the differential toxicity of $PM_{2.5}$ constituents and their potential influence on the long-term health effects of $PM_{2.5}$.

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Table 1. Summary statistics for each variable. For population size at risk, mortality count and long-term (previous 1-year average) PM_{2.5}, location-specific monthly values are averaged across locations for the whole study period (2000-2006). For chemical constituents, location-specific 7-year averages are averaged across locations. For community-level confounders, location-specific values are averaged across locations.

Variable		Complete Case Data (n=241) Mean \pm Std Dev	All Sites Data (n=518) Mean \pm Std Dev
Population size at risk (#/month)		16901.00 \pm 17307.31	14538.92 \pm 15453.71
Mortality count (#/month)		76.01 \pm 74.04	64.93 \pm 66.7
Long-term PM _{2.5} exposure level ($\mu\text{g}/\text{m}^3$)		14.56 \pm 1.88	13.7 \pm 2.13
PM _{2.5} chemical constituents ($\mu\text{g}/\text{m}^3$)	Elemental carbon (EC)	0.71 \pm 0.33	0.68 \pm 0.24*
	Organic carbon matter (OCM)	4.1 \pm 1.06	4.05 \pm 0.90*
	Sulfate (SO ₄ ⁻)	4.22 \pm 0.81	4.14 \pm 0.80*
	Silicon (Si)	0.09 \pm 0.03	0.09 \pm 0.03*
	Nitrate (NO ₃ ⁻)	1.86 \pm 0.86	1.68 \pm 0.85*
	Sodium (Na)	0.16 \pm 0.08	0.17 \pm 0.07*
Community-level confounders	Family income (\$)	38247.39 \pm 11149.87	40305.00 \pm 12461.21
	% high school graduate ^a	0.78 \pm 0.06	0.79 \pm 0.08
	% urban ^b	0.93 \pm 0.16	0.86 \pm 0.23
	% white ^c	0.64 \pm 0.20	0.70 \pm 0.20
	% black ^d	0.25 \pm 0.18	0.19 \pm 0.17

*Numbers are calculated including the imputed PM_{2.5} constituent levels for the 277 PM_{2.5} with missing constituent levels.

^aThe proportion of people with high school diploma or equivalent. ^bThe proportion of residents in urban environment. ^cThe proportion of white residents. ^dThe proportion of black residents.

Figure Legends

Figure 1. Map of 518 PM_{2.5} monitor locations and 174 PM_{2.5} chemical constituent monitor locations in the Eastern Region of the US.

Figure 2a. Map of 7-year (2000-2006) averages of monthly long-term (previous 1-year average) PM_{2.5} exposure ($\mu\text{g}/\text{m}^3$) for all PM_{2.5} monitor locations (n=518).

Figure 2b. Map of 7-year (2000-2006) averages of monthly mortality rate (deaths/month/1000persons) for all PM_{2.5} monitor locations (n=518).

Figure 3. Maps of 7-year (2000-2006) averages of each of the 6 PM_{2.5} chemical constituents ($\mu\text{g}/\text{m}^3$) for 241 monitor locations with available data

Figure 4a. Map of the estimates (posterior means) of the spatially-varying (SV) intercept from the complete case data analysis (n=241, left) and the all sites data analysis (n=518, right). The values represent the monthly mortality rate (deaths/month/1000persons) when previous-year PM_{2.5} is at location-specific average.

Figure 4b. Map of the estimates (posterior means) of the spatially-varying (SV) slope from the complete case data analysis (n=241, left) and the all sites data analysis (n=518, right). The values represent the % increase in the monthly mortality rate associated with 1 $\mu\text{g}/\text{m}^3$ increase in previous-year PM_{2.5}.

Figure 5a. Posterior estimates with 95% posterior intervals for the β_k regression coefficients in the second-level SV intercept model. Left-solid bars are for the complete case data (n=241) and right-dashed bars are for the all sites data (n=518). Values correspond to the estimated percentage increase in monthly mortality rate associated with a 1-SD increase in each constituent, adjusted for previous-year average of PM_{2.5} total mass and for community-level covariates.

Figure 5b. Posterior estimates with 95% posterior intervals for the γ_k regression coefficients in the second-level SV slope model. Left-solid bars are for the complete case data (n=241) and right-dashed bars are for the all sites data (n=518). Values correspond to the estimated percentage increase in the association between previous-year average of PM_{2.5} and mortality

when combined with a 1-SD increase in each constituent, adjusted for community level covariates.

Figure 1. Map of 518 PM_{2.5} monitor locations and 174 PM_{2.5} chemical constituent monitor locations in the Eastern Region of the US.

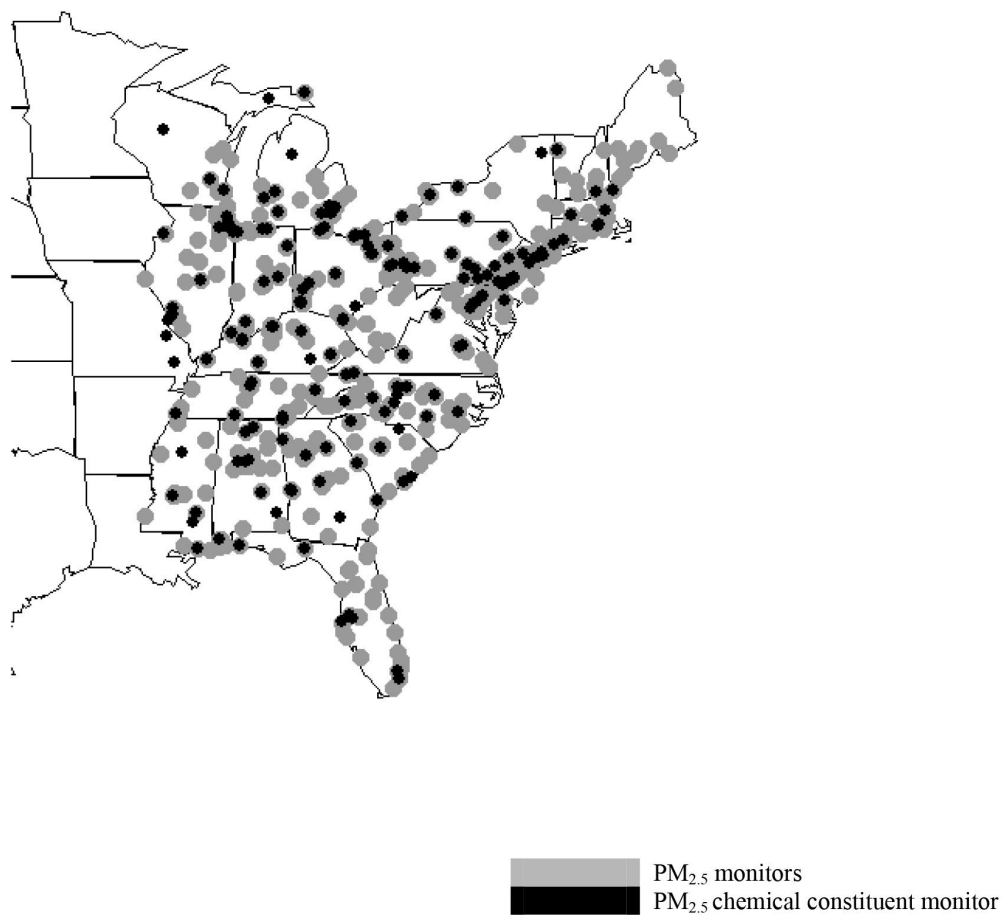


Figure 2a. Map of 7-year (2000-2006) averages of monthly long-term (previous 1-year average) $\text{PM}_{2.5}$ exposure ($\mu\text{g}/\text{m}^3$) for all $\text{PM}_{2.5}$ monitor locations (n=518).

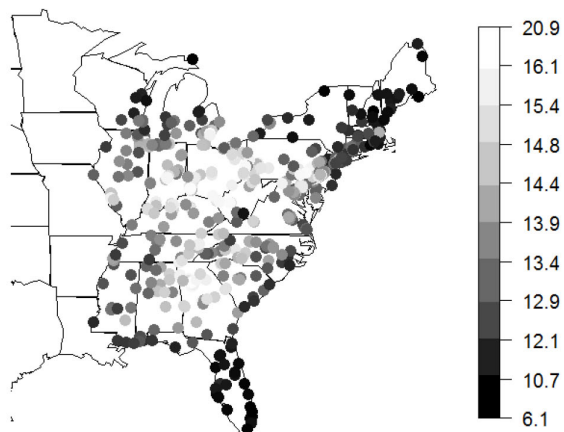


Figure 2b. Map of 7-year (2000-2006) averages of monthly mortality rate (deaths/month/1000persons) for all $\text{PM}_{2.5}$ monitor locations (n=518).

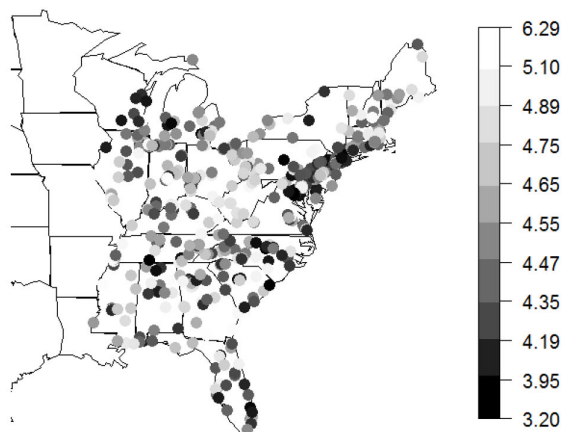


Figure 3. Maps of 7-year (2000-2006) averages of each of the 6 PM_{2.5} chemical constituents ($\mu\text{g}/\text{m}^3$) for 241 monitor locations with available data.

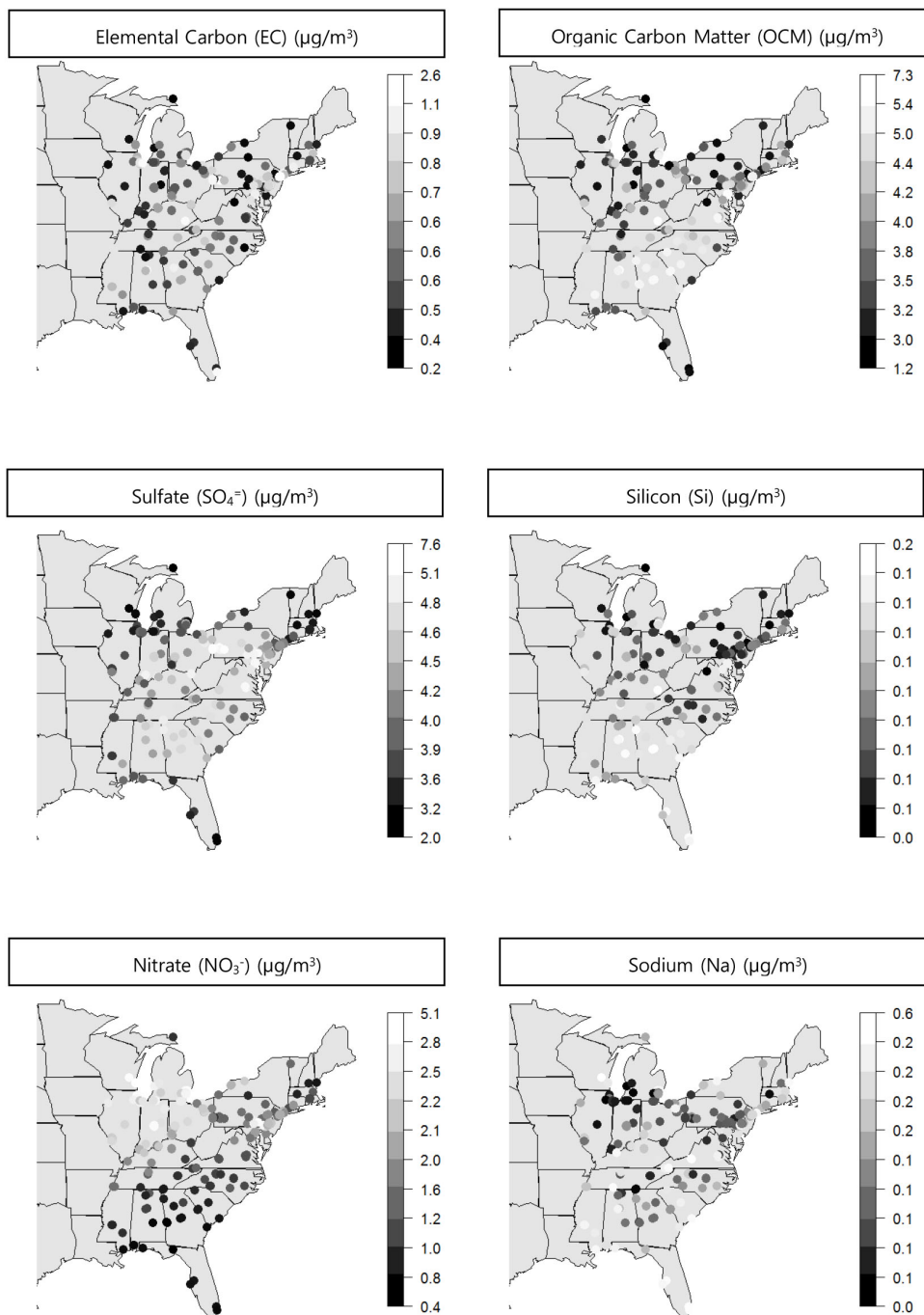


Figure 4a. Map of the estimates (posterior means) of the spatially-varying (SV) intercept from the complete case data analysis (n=241, left) and the all sites data analysis (n=518, right). The values represent the monthly mortality rate (deaths/month/1000persons) when previous-year $PM_{2.5}$ is at location-specific average.

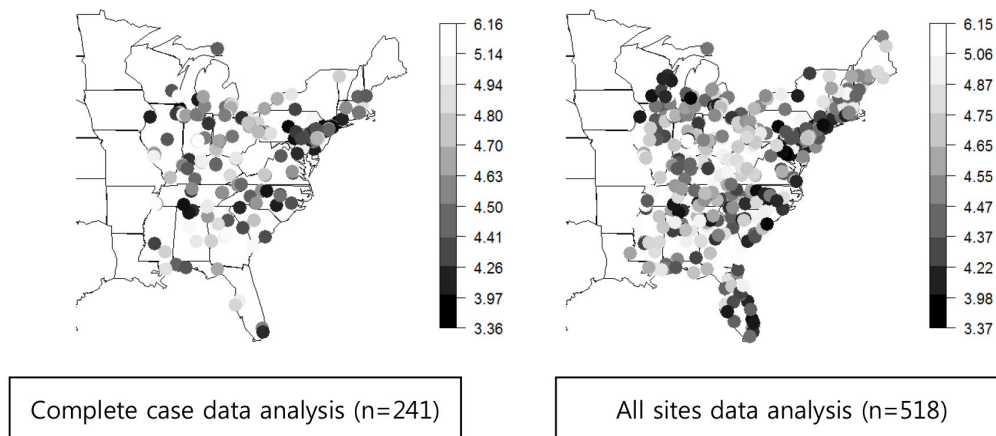


Figure 4b. Map of the estimates (posterior means) of the spatially-varying (SV) slopes from the complete case data analysis (n=241, left) and the all sites data analysis (n=518, right). The values represent the % increase in the monthly mortality rate associated with $1 \mu g/m^3$ increase in previous-year $PM_{2.5}$.

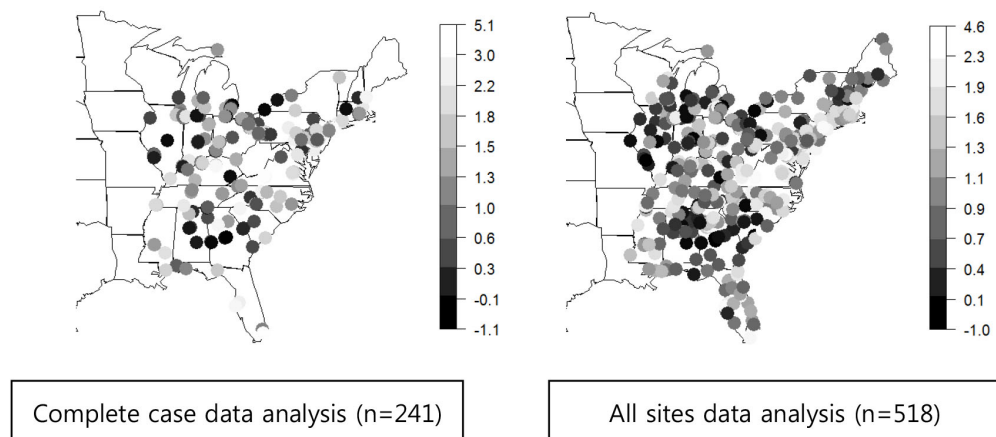


Figure 5a. Posterior estimates with 95% posterior intervals for the β_k regression coefficients in the second-level SV intercept model. Left-solid bars are for the complete case data (n=241) and right-dashed bars are for the all sites data (n=518). Values correspond to the estimated percentage increase in monthly mortality rate associated with a 1-SD increase in each constituent, adjusted for previous-year average of $PM_{2.5}$ total mass and for community-level covariates.

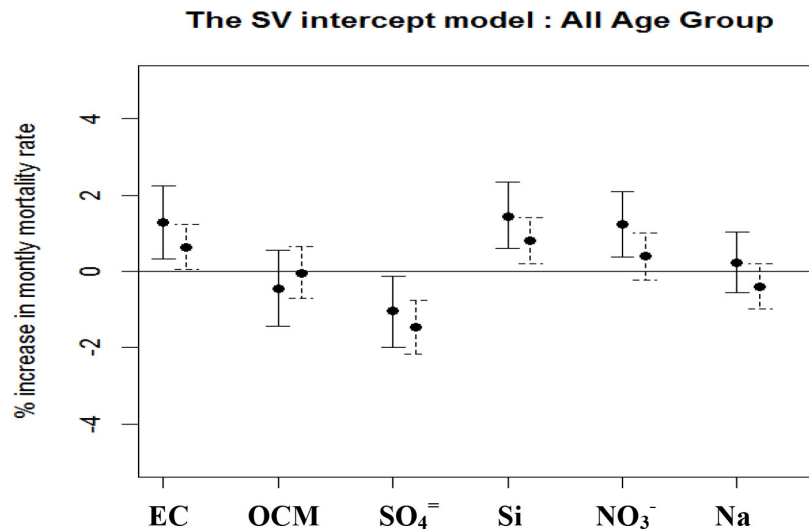


Figure 5b. Posterior estimates with 95% posterior intervals for the γ_k regression coefficients in the second-level SV slope model. Left-solid bars are for the complete case data (n=241) and right-dashed bars are for the all sites data (n=518). Values correspond to the estimated percentage increase in the association between previous-year average of $PM_{2.5}$ and mortality when combined with a 1-SD increase in each constituent, adjusted for community level covariates.

